

AMENDMENTS TO THE CLAIMS

Claim 1 (original). A modified human Factor VIII molecule being substantially non-immunogenic or less immunogenic than non-modified human Factor VIII and having essentially the same biological specificity and activity when used in vivo, comprising specifically altered amino acid residues compared with the non-modified parental molecule, wherein said altered amino acid residues cause a reduction or an elimination of one or more of T-cell epitopes which act in the parental non-modified molecule as MHC class II binding ligands and stimulate T-cells.

Claim 2 (original). A modified Factor VIII molecule according to claim 1, wherein said alterations are made at one or more positions within one or more of the strings of contiguous amino acid residues present in the parental molecule as depicted in Table 1.

Claim 3 (original) A modified Factor VIII molecule according to claim 2, wherein said alterations are made at one or more positions within one or more of the strings of contiguous amino acid residues present in the parental molecule as depicted in Table 2.

Claim 4 (currently amended). A modified Factor VIII molecule according to ~~any of the claims 1 to 3~~ claim 1, wherein said alterations are substitutions of 1 - 9 amino acid residues.

Claim 5 (currently amended). A modified Factor VIII molecule according to claim 4, wherein one, more or all of the amino acid residues at the following positions of SEQ ID NO: 73 in a sequence string as depicted in Table 1 has been substituted:
197, 198, 199, 201, 202, 407, 411, 412, 419, 515, 517, 613, 617, 636, 637, 638, 639, 823, 1011, 1013, 1208, 1209, 1210, 1254, 1255, 1257, 1262, 1264, 1268, 1119, 1120, 1121, 1122, 1123.

Claim 6 (currently amended). A modified Factor VIII molecule according to claim 3, wherein in string P10 (residues 1009-123 of SEQ ID NO: 73) ~~of Table 2~~ one, more or all of the following amino acid residue substitutions has been carried out:

I1208A, I1208T, I1208N;

I1209C;

M1210K, M1210N.

Claim 7 (currently amended). A modified Factor VIII molecule according to claim 3, wherein in peptide P8 (residues 1204-1218 of SEQ ID NO: 73) ~~of Table 2~~ one, more or all of the following amino acid residue substitutions has been carried out:

M1013K;

~~I1011A, I1011C, I1011D, I1011E, I1011G, I1011H, I1011K, I1011P, I1011Q, I1011R, I1011S,~~

~~I1011T~~ I1011A, I1011C, I1011D, I1011E, I1011G, I1011H, I1011K, I1011P, I1011Q,

I1011R, I1011S, I1011T.

Claim 8 (currently amended). A modified Factor VIII molecule according to claim 3, wherein in peptide P7 (residues 817-831 of SEQ ID NO: 73) ~~of Table 2~~ one, more or all of the following amino acid residue substitutions has been carried out:

V823A, V823D, V823E, V823G, V823H, V823N, V823P

V823S, V823T.

Claim 9 (currently amended). A modified Factor VIII molecule according to ~~any~~ claim 1, wherein when tested as a whole protein in a biological assay of induced cellular proliferation of human T-cells exhibits a stimulation index (SI) smaller than the parental molecule and smaller than 2 tested in parallel using cells from the same donor wherein said index is taken as the value of cellular proliferation scored following stimulation by the protein and divided by the value of cellular proliferation scored in control cells not in receipt of protein and wherein cellular proliferation is measured by any suitable means.

Claim 10 (cancelled).

Claim 11 (currently amended). A pharmaceutical composition comprising a modified Factor VIII molecule of ~~any of the preceding claims~~ claim 1, optionally together with a pharmaceutically acceptable carrier, diluent or excipient.

Claim 12 (original). A peptide molecule selected from Table 1 having a potential MHC class II binding activity and created from the primary sequence of non-modified human Factor VIII, whereby said peptide molecule has a stimulation index of > 1.8 in a biological assay of cellular proliferation, wherein said index is taken as the value of cellular proliferation scored following stimulation by a peptide and divided by the value of cellular proliferation scored in control cells not in receipt peptide and wherein cellular proliferation is measured by any suitable means.

Claim 13 (original). A modified peptide molecule deriving from the peptide molecule of claim 12 by amino acid substitution, having a reduced or absent potential MHC class II binding activity expressed by a stimulation index of less than 2, whereby said index is taken as the value of cellular proliferation scored following stimulation by a peptide and divided by the value of cellular proliferation scored in control cells not in receipt peptide and wherein cellular proliferation is measured by any suitable means.

Claims 14 - 16 (cancelled).

Claim 17 (new). An isolated polypeptide, which is a modified human Factor VIII molecule, the isolated polypeptide being substantially non-immunogenic or less immunogenic than wild-type human Factor VIII, and having essentially the same biological specificity as wild-type human Factor VIII when used *in vivo*, the isolated polypeptide having the amino acid residue sequence of SEQ ID NO: 73, but including at least one specific amino acid residue substitution in SEQ ID NO: 73, wherein said amino acid residue substitution eliminates at least one T-cell epitope present in wild-type human Factor VIII.

Claim 18 (new). An isolated polypeptide of claim 17, wherein at least one of the amino acid residues at the following positions of SEQ ID NO: 73 has been substituted for a different amino acid than is present in the amino acid residue sequence of the wild type human Factor VIII: 197, 198, 199, 201, 202, 407, 411, 412, 419, 515, 517, 613, 617, 636, 637, 638, 639, 823, 1011, 1013, 1208, 1209, 1210, 1254, 1255, 1257, 1262, 1264, 1268, 1119, 1120, 1121, 1122, and 1123.

Claim 19 (new). An isolated polypeptide of claim 17, wherein the amino acid residue sequence of the polypeptide includes at least on one amino acid residue substitution in SEQ ID NO: 73 selected from the group consisting of: M1013K, I1011A, I1011C, I1011D, I1011E, I1011G, I1011H, I1011K, I1011P, I1011Q, I1011R, I1011S, and I1011T.

Claim 20 (new). An isolated polypeptide of claim 17, wherein the amino acid residue sequence of the polypeptide includes at least on one amino acid residue substitution in SEQ ID NO: 73 selected from the group consisting of: V823A, V823D, V823E, V823G, V823H, V823N, V823P, V823S, and V823T.

Claim 21 (new). An isolated polypeptide of claim 17, wherein the amino acid residue sequence of the polypeptide includes at least on one amino acid residue substitution in SEQ ID NO: 73 selected from the group consisting of: I1208A, I1208T, I1208N, I1209C, M1210K, and M1210N.

Claim 22 (new). An isolated DNA molecule encoding a polypeptide of claim 1.

Claim 23 (new). An isolated DNA molecule encoding a polypeptide of claim 17.

Claim 24 (new). A pharmaceutical composition comprising a polypeptide of claim 17 together with a pharmaceutically acceptable carrier, diluent or excipient.